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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/668,663	09/23/2003	Victor C. Yang	30275/40871	5598

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EXAMINER	
ROBINSON, HOPE A	
ART UNIT	PAPER NUMBER
1652	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/668,663	YANG ET AL.	
	Examiner	Art Unit	
	HOPE A. ROBINSON	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 January 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *48-50,55-68 and 70-75* is/are pending in the application.

4a) Of the above claim(s) *57 and 58* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *48-50,55,56 and 59-68* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 January 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Application Status

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on January 9, 2009 has been entered.

Claim Disposition

2. Claims 48-50, 55-68 and 70-75 are pending. Claims 48-50, 55-56 and 59-68 and 70-75 are under examination.

Maintained-Specification Objection

3. The specification is objected to because of the following informalities:

As previously stated, the specification is objected to because trademarks are disclosed throughout the instant specification and not all of them are capitalized or accompanied by the generic terminology. The use of the trademarks such as TWEEN-20®, for example, have been noted in this application (see page 62). It should be capitalized wherever it appears and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary

nature of the marks should be respected and every effort made to prevent their use in any manner, which might adversely affect their validity as trademarks.

Correction of the above is required.

Claim Objection

4. The claims are objected to because of the following informalities:

Claims 48-50 and 59-63 are objected to for improper dependency.

Claim 63 as amended is objected to for the recitation of and extraneous period (.)

Correction is required.

Maintained and Amended-Claim Rejections - 35 USC 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 48-50, 55-56, 59-68, 70-71 and 73-75 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that

the inventor(s), at the time the application was filed, had possession of the claimed invention.

The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject matter later claimed by him. The courts have stated:

"To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997); In re Gostelli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966."Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In *Regents" of the University of California v. Eli Lilly & Co.* the court stated:

"A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure,

formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *Fiers,* 984 F.2d at 1171, 25 USPQ2d 1601; *In re Smythe,* 480 F.2d 1376, 1383, 178 USPQ 279, 284985 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus ...") *Regents" of the University of California v. Eli Lilly & Co.,* 43 USPQ2d 1398.

The MPEP further states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP § 2163. The MPEP does state that for a generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. MPEP § 2163. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP § 2163. Although the MPEP does not define what constitute a sufficient number of representative species, the courts have indicated what do not constitute a representative number of species to adequately describe a broad generic. In *Gostelli,* the courts determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. *In re Gostelli,* 872, F.2d at 1012, 10 USPQ2d at 1618. The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the Application. These

include "level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient." MPEP § 2163. While all of the factors have been considered, a sufficient amount for *a prima facie* case is discussed below.

Further, to provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include: a) the scope of the invention; b) actual reduction to practice; c) disclosure of drawings or structural chemical formulas; d) relevant identifying characteristics including complete structure, partial structure, physical and/or chemical properties, and structure/function correlation; e) method of making the claimed compounds; f) level of skill and knowledge in the art; and g) predictability in the art.

The claimed invention is directed to a method of inactivating heparin or low molecular weight heparin with a composition comprising an amount of at least a purified protamine fragment effective to inactivate heparin or low molecular weight heparin. The claims recite that the fragment is bioactive and has a molecular weight of between about 400 and about 2500 Daltons. There is no indication of which purified protamine fragment the claimed invention is directed to (see claim 55 for example). The art recognizes, salmon, human, mouse, culpeine protamines for example. Independent

claim 55 does not establish whether the native protamine used as a comparison is mammalian or another organism. No identified source as to where the protamine is derived from is provided in the claim to guide one of ordinary skill in the art to determine where the recited fragment is from and the composition of amino acids. Vilfan et al. (J. Biol. Chem., 2004, May 7, vol. 279 (19), pages 20088-95, see abstract) disclose that mammalian protamine can be divided into three domains, a central DNA binding domain that is arginine-rich, an amino and a carboxyl-terminal domains that are rich in cysteine residues. Note that claim 74 is directed to a fragment comprising five or six arginine and one proline. There are protamines reported in the art that do not have a proline or glycine. In addition, claim 72 recites that the fragment is a protease cleavage product and lists ficin, thermolysin, collagenase, kallikrein and proline-specific endopeptidase which would produce different fragments based on the cleavage sites.

Further, Chang et al. (AAPS Pharm Sci, 2001, vol. 3(3), article 17, DOI: 10, 1208ps03017) disclose that an octapeptide CR_7 was synthesized in both monomeric and dimeric forms and tested in its ability to neutralize heparin. Moreover, the instant specification provides several reasons why thermolysin would not be a preferred method of cleavage. Therefore absent adequate guidance in the specification with respect to the fragments of the claimed invention by way of a structure-function correlation the ordinary skilled artisan could not reasonably conclude that applicant's were in possession of the genus of fragments encompassed in the claims.

Additionally, claim 67 for example is directed to a first and second protamine, which provides evidence that there can be more than one protamine fragments,

however, no structure is provided. In addition the claims are directed to a method that utilizes the undefined protamine and a coagulant (see claim 63), which is also undefined. Furthermore, the art teaches that protamine given to neutralize heparin after extracorporeal circulation can trigger a catastrophic reaction in some patients (see Tan et al. Anesthesiology, Feb. 1989, vol. 70, no. 2, pages 267-75). Therefore, the claimed invention needs to adequately describe the protamine fragment intended in the method. Thus the claims lack adequate written description to demonstrate to a skilled artisan that applicant was in possession of the claimed invention. It is noted that claims such as claims 74 and 75 recites 5 or 6 arginine residues and even 1 proline. A proline combined with 6 arginine results in a molecular weight of 1159 daltons and it is unclear what other residues would be encompassed in the structure to make up the remaining weight in the protein structure to achieve the recited "about 2500 Daltons", absent guidance. Therefore, a biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence. For example, even though a genetic code table would correlate a known amino acid sequence with a genus of coding nucleic acids, the same table cannot predict the native, naturally occurring nucleic acid sequence of a naturally occurring mRNA or its corresponding cDNA. *See MPEP 2163.*

Further, *Vas-Cath Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir.1991)*, states that "applicant must convey with reasonable clarity to those

skilled in the art that, as of the filing date sought, he or she was in *possession of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*" (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at page 1116). The skilled artisan cannot envision the detailed chemical structure of the encompassed genus of encoded proteins, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. *See Fiers v. Revel, 25 USPQ2d 1601 at 1606 (CAFC 1993). See MPEP 2163.*

Therefore, for all these reasons the specification lacks adequate written description, and one of skill in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

Response to Arguments

6. The response filed has been considered in full. Note that the objection over the specification remains as applicant state that amendment will not be provided until an allowance notification is obtained. The rejection under 35 U.S.C. 112 first paragraph has been maintained.

Regarding the maintained rejection under 35 U.S.C. 112, first paragraph applicant traverses the rejection and points to Example 1 in the instant specification. For convenience the text of the example is provided below:

> In this example, low molecular weight protamine (LMWP) fragments were derived from native protamine by enzymatic digestion of protamine with thermolysin. Then, the heparin-neutralizing ability of the LMWP fragments was examined in vitro, using a electrochemical sensor method and various biological assays. Next, the immunogenicity and antigenicity of the 10
> LMWP species were examined in mice, using an appropriately selected enzyme-linked immunosorbent assay (ELISA). The enzymatic digestion of protamine yields LMWP that contained anti-heparin activity but lacked antigenicity and immunogenicity.

Note that the example does not provide the derivation of the "native protamine" and the art shows so many different types of protamine and with different structures, for example protamines with glycine or without, with proline or without, with threonine etc. To obtain the molecular weight range and the protamine fragment of the invention guidance is needed as to what organism and what composition of amino acids are contained in the claimed fragment. Essentially a structure-function correlation is needed. Applicant state that claims 72 and 73 should be allowable if the protease used is important to determine the fragment of the protamine. The protease used is important as it will give a glimpse of what the structure will look like in knowing where the protease cuts. However, the aforementioned claims are not presently allowable as the thermolysin for example is disclosed in the specification as being problematic (producing fragments that may be toxic) and proline-specific endopeptidase cuts specifically at a proline, and some protamine do not have a proline residue, thus it is unclear what organism to determine if this protease could be used, or did applicants modified the native protamine and then further modified the structure to be able to use

that protease, for example addition of a proline to the native structure and then cutting it with the proline-specific endopeptidase. Applicant states that claims 74 and 75 recite structural amino acids residues in the fragment. The claims recite 5 or 6 arginine and 1 proline, however based on the open claim language it is unclear what else the fragment contains. The claims do not set forth for example "a fragment comprising the amino acid sequence of Arg-Arg-Arg-Arg-Arg-Arg-Pro SEQ ID NO:5". The issue at hand is that what fragment is going to maintain the activity of the native. No structural limitations are provided in the claim as to what said fragment looks like. The claimed protamine is modified to achieve the reduced immunoresponsiveness or toxicity, however, the claims do not establish what those modifications are. It is noted that the specification at paragraph [0109] discloses that ficin a plant protease cleaves protamine at the C-end and results in lower toxicity, however, the limitations of the specification cannot be read into the claims. Therefore, a skilled artisan would not be able to envision the detail chemical structure of the genus of protamine fragments encompassed in the claims. The art recognizes that one protamine structure comprises 31 amino acids per molecule and only five types of residues: arginine (20), glycine (6), serine (3), alanine (1) and tyrosine (1). The primary structure of protamine is reported and the N-terminal sequence contains the four hydroxylated amino acids of the molecule; the C-terminal region shows a sequence of eleven adjacent residues of arginine and contains all the glycine residues present in the protein. However, there is no indicia as to where in the native structure modifications will occur such that the resultant effect is a fragment of protamine that has

reduced immunoresponsiveness or toxicity and will inactive heparin or LMW heparin. Thus, the claims encompass a genus of fragments not adequately described.

It is noted that applicant argues that the structure is well established, however, the fragments are claimed and they are not adequately described. It is noted that newly submitted claims 71-72 addresses enzymatic cleavage of the protamine which would give a skilled artisan a glimpse of what the structure would look like based on the enzymes used, for example thermolysin which cuts at the N-terminal or ficin which cuts at the C-terminal. However, this limitation is not recited in the independent claim. Applicant is urged to be explicit in which protease is used since the specification discloses at paragraph 0108 and 0109 the disadvantages/advantages (specifically thermolysin is not preferred) of each and indicates that ficin is preferred. For example, claim 55 recites "at least a purified protamine fragment effective to inactivate heparin or low molecular weight heparin; wherein said purified protamine fragment is bioactive, has a molecular weight of between about 400 and about 2500 Daltons as determined by gel filtration and has reduced immunoresponsiveness or toxicity compared to native protamine", however, no correlation is made between function and structure. As stated about a skilled artisan cannot envision the detailed chemical structure of the claimed genus of protamine fragments. Thus, the rejection remains.

Conclusion

7. No claims are presently allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Hope A. Robinson whose telephone number is 571-272-0957. The examiner can normally be reached on Monday-Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Nashaat Nashed, can be reached at (571) 272-0934. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Hope A. Robinson/

Primary Examiner, Art Unit 1652